Date: November 7, 2001

From: Gibbes Johnson

To: BLA #99-1470 File, Our STN: BL 103946/0 (replaces Ref. No. 99-1470)

Through: Amy Rosenberg, M.D., Barry Cherney, Ph.D. GSR 11/14/01

Subject: Review of Amendment #~~18~~ 5014 received on July 27, 2001. The second CR letter dated August 30, 2001 repeated items #1, 4 and 7 from the first CR letter due to an inadequate sponsor response. Please see the review memo dated July 12, 2001 for the review of the first CR letter and the initial responses to these items. Based upon a telecon with the sponsor on July 19, 2002 the sponsor addressed these issues in Amendment #18.
The CR letter questions/issues (#1, 4 and 7) are followed by my assessment of the sponsor's response.

1. The assay for urate oxidase enzyme activity, used as a release test and in stability studies, is not performed under conditions which allow for a valid evaluation of the critical kinetic parameters of the test sample enzyme relative to the reference standard.

   a. Please develop an assay which is performed under the conditions of steady state kinetics, such that an initial velocity (rate) is measured and substrate concentrations do not significantly change during the course of the reaction (i.e., < 5% of substrate is converted to product). This assay should monitor the initial velocity of the reaction over a broad range of substrate concentrations. The results of this analysis should confirm that the test sample enzyme possesses comparable values for the [redacted] relative to the reference standard enzyme.

b. Please submit data from the revised assay for urate oxidase activity which support the conclusion that the enzymatic activity of drug substance production batches in the BLA are consistent and comparable to the primary and/or working reference standard.

Reviewer's assessment of response:

Sanofi-Synthelabo agrees to conduct the assay for urate oxidase enzyme activity using the [redacted] method initially described in the Response to the BLA Action Letter dated February 27, 2001, for release testing of production batches including launch materials and subsequent stability studies. As agreed upon, the method will include the calculation of the [redacted] for each batch relative to the working reference material.

Each working reference material will be tested against the primary reference material according to this method, using the same acceptance criteria as for the drug substance. Provisional acceptance criteria have been established for drug substance and drug product based on the results obtained for the three drug substance validation batches, the working reference material and the primary reference material. Sanofi-Synthelabo proposes the following post-approval commitments: complete complementary validation of the method by the end of October 2001 (report available in November 2001); release control of batches intended for marketing using the new method with a range of substrate concentrations; review of provisional acceptance criteria on the basis of additional data, and submission of the revised acceptance criteria and complete validation package by February 2002. **This response is acceptable.**

4. Release testing focuses primarily on an analysis of drug substance [redacted] with little attention given to addressing [redacted]

[redacted] To address these concerns:

a. Please include an evaluation of the complete [redacted] as part of the acceptance criteria for release tests.

b. In the [redacted] analysis used as a release and in-process test, please include an additional [redacted] to confirm the absence of [redacted]

c. Similarly, in the [redacted] please include an additional [redacted]

Reviewer's assessment of response:

The sponsor agrees to introduce the additional [redacted] analysis as part of release of the drug substance and in [redacted] as part of in-process testing. Necessary action steps will be taken when the limits are exceeded, to characterize the difference observed before any release of batch. For both methods, an evaluation of the complete [redacted] will be included in the acceptance criteria with a special focus on the [redacted] and on the part corresponding to the additional [redacted] The monographs and procedures will be revised accordingly. Provisional limits were provided, based on the results of the three validation batches provided in the response package.

Release tests:

For both methods, a [redacted] (at the same molarity as the corresponding test solution) is introduced. This allows a more accurate comparison at the [redacted] between the test solution [redacted] and the blank [redacted]

[redacted]

"Evaluate the complete test [redacted] in comparison with the blank run and the working reference material [redacted] The positive quantifiable [redacted] are not higher than [redacted] If any additional [redacted] is seen in the rest of the [redacted] compared to the blank run and the reference working material [redacted] its intensity is not more than the quantification limit of the method"

[redacted]

"Evaluate the complete test [redacted] in comparison with the blank run and the working reference material [redacted] The positive quantifiable [redacted] are not higher than [redacted] If any additional [redacted] is seen in the rest of the [redacted] compared to the blank run and the reference working material [redacted] its intensity is not more than the quantification limit of the method"

<u>In-Process Testing:</u>

A similar strategy will be applied for the in-process control by [redacted] after purification step 4. A provisional action limit is proposed:

"Evaluate the complete test [redacted] in comparison with the blank run and the pool 4 reference material [redacted] The positive quantifiable [redacted] are not higher than [redacted] and the pool 4 reference material [redacted] If any additional [redacted] is seen in the rest of the [redacted] its intensity is not more than the quantification limit of the method"

These tentative limits will be finalized after [redacted] from at least [redacted] batches

produced over the next several months will be analyzed. Complementary validation of the modified methods will be performed as well and data provided along with the revised limits by January 2002. **This response is acceptable.**

7. In all [redacted] release tests for the drug product, please include a control analysis of excipient alone. The acceptance criteria should include a consideration of potential impurities and related substances which [redacted]

Reviewer's assessment of response:

The evaluation of the [redacted] will be included as part of the acceptance criteria, for [redacted] The initial analysis of [redacted] commercial batches will be expanded to at least [redacted] batches in order to define a robust acceptance criteria. For this, as specified previously, the test [redacted] will be compared with a reference [redacted] and a blank [redacted] However, in order to perform a more accurate comparison, Sanofi-Synthelabo will adopt the proposal of the FDA, that is to [redacted] excipient alone. Provisional limits are provided, based on the results of the [redacted] validation batches that were included in the February 2001 response package. Necessary action steps will be taken when the limits are exceeded, to characterize the difference observed before any release of batch.

Provisional limits are established as follows:
"Evaluate the test [redacted] in comparison with a control analysis with the excipient alone. The positive [redacted] are not higher than [redacted]

A complementary validation of the method will be performed as well. The sponsor committed to provide post-approval the validation and the finalized limits at the same time as for Question 4 (by the end of January 2002). **This response is acceptable.**